

# **EXHIBIT A**

Docket No.: A0039.0001  
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:  
Sorana Greiveldinger-Poenaru et al.

Application No.: 10/563,938

Confirmation No.: 3285

Filed: January 10, 2006

Art Unit: 1624

For: NOVEL BENZOFURAN DERIVATIVES

Examiner: D.R. Rao

**DECLARATION OF DR. STEPHEN HAWSER UNDER 37 C.F.R. § 1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

I, Dr. Stephen Hawser, do hereby declare and state:

1. I am presently a scientist employed as consultant by Arpida AG, assignee of the above-identified patent application.
2. My academic background, technical experience and list of publications are set forth in my curriculum vitae, attached hereto as Exhibit 1.
3. I have read and am familiar with the subject application, including the claims pending.
4. I have read and am familiar with the June 24, 2008 Non-Final Office Action issued by the U.S. Patent and Trademark Office concerning the subject application. I understand that in the Non-Final Office Action, the Examiner rejected claims 1-6, 8, 16 and 18-23 under 35 U.S.C. § 103(a) as being allegedly

obvious over Burri et al. (PCT International Publication No. WO 02/10156; hereinafter "Burri et al.").

5. I understand that as a basis for this rejection, the Examiner asserts that the claimed compounds differ from the disclosed reference compounds in Burri et al. by having the indolyl group attached via a position different from the reference compounds, *i.e.*, at the 3-position as compared to the reference compound which is attached through the 1-position. The Examiner also asserts that the claimed compounds are positional isomers of the reference compounds, and that a person having ordinary skill in the art would have been motivated to prepare the claimed compounds because such isometric compounds are suggestive of one another and would be expected to share similar properties and therefore, the same use as taught for the reference compounds, *i.e.*, as antibacterial agents. The Examiner further asserts that absent unexpected results, a compound which is structurally isometric with a compound of the prior art are *prima facie* obvious.

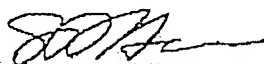
6. I and/or individuals under my direction performed the following experiments to obtain and compare minimal inhibitory concentrations ("MIC") results between claimed compounds of the present invention and compounds disclosed in Burri et al. Specifically, antimicrobial susceptibility testing, as described in "General Procedure E: Measurement of antimicrobial activity" on PCT International Publication No. WO 2005/005418 (which is also on page 20, ll. 1-9 of the subject application), was conducted on exemplary compounds of the present invention and the compounds of Burri et al. (*see* page 1, lines 28-30). A copy of the relevant pages of PCT International Publication No. WO 2005/005418 is attached hereto as Exhibit 2. ATCC *Streptococcus pneumoniae* 49619 bacterial strain was used during the antimicrobial susceptibility testing.

7. The identity of the compounds tested, as well as the results of the antimicrobial susceptibility tests of exemplary compounds of the present invention in comparison with the compounds disclosed in Burri et al. are attached hereto as Exhibit 3.

8. As shown in Exhibit 3, the results of the susceptibility tests indicate that exemplary compounds of the present invention have significantly superior antibacterial activity as compared to the compounds disclosed in Burri et al.

I hereby declare that all statements made in herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the subject application or any patent issuing thereon.

Dated: 20/10/2004

  
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Dr. Stephen Hawser

# **EXHIBIT 1**

## **CURRICULUM VITAE**

### **STEPHEN HAWSER, Ph.D.**

#### **PROFILE**

Senior Scientist / Senior Manager with international experience in the pharmaceutical and biotechnology sectors in terms of research and development of new chemical entities and in the project management of projects both in early and more advanced levels.

Responsibilities have included a strong involvement in internal and external non-clinical microbiology & non-clinical pharmacology /toxicology, in clinical trials & clinical microbiology, preparation of INDs, NDA and MAA. Additionally involved in the preparation of relevant material for discussions with regulatory authorities (FDA & EMEA) and with microbiology regulators (CLSI & EUCAST) and in the scientific evaluation of products/molecules for in-licensing purposes and competitive analysis.

A strong scientific background that has been exploited in building powerful interpersonal skills including problem solving, forward thinking, planning and decision making. Experienced in budgeting and project management.

Furthermore, significant experience in fund-raising in a local and international environment with banks and investment groups.

An international character fluent in three languages having worked in Italy, France and Switzerland.

#### **ADDRESSES**

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Professional:                      Arpida AG, Reinach, Switzerland.

#### **HIGHER EDUCATION**

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1988 - 1992: University of Dundee, UK.  
Doctor of Philosophy (Ph.D.). Thesis Title: "Characterization of the toxicity of the cyanobacterium Oscillatoria spp. from fresh- and marine waters".

1984 - 1988: University of Aberdeen, Department of Microbiology, UK  
Bsc (honours) microbiology, upper second class

## WORK EXPERIENCE

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July 2008 to present: Consultant, Arpida AG, Reinach

August 2005 to June 2008: Director of Microbiology  
Arpida AG, Reinach, Switzerland

Responsibilities have included a strong involvement in internal and external non-clinical microbiology & non-clinical pharmacology /toxicology, in clinical trials & clinical microbiology, preparation of INDs, NDA and MAA. Additionally involved in the preparation of relevant material for discussions with regulatory authorities (FDA & EMEA) and with microbiology regulators (CLSI & EUCAST) and in the scientific evaluation of products/molecules for in-licensing purposes and competitive analysis.

Aug. 2001 to July 2005: Director of Biology  
Arpida AG, Muenchenstein, Switzerland

Responsible for all biological aspects related to the development of the company's most advanced compound, Iclaprim.

Responsible for the development of early stage compounds from screening to the identification and profiling of hit compounds and their further development to being identified as potential lead series. Analyses of SAR data and the active involvement in using this data for further advancement of projects.

Responsible for the scientific evaluation of products and new molecules for eventual in-licensing and for competitive profile analyses of such products / molecules versus current standards of therapy.

Jan. 2001 – July 2001: Head Microbiology Laboratory  
Arpida AG

Sept. 1999 – Oct. 2000: GlaxoWellcome, Verona, Italy. Senior Scientist.

Responsibilities:

Responsible for the development of novel models for the determination of in vitro PK/PD profiles of new chemical entities.

Nov. 1996- Sept. 1999: Hoechst Marion Roussel, Romainville, France.  
Head of Laboratory of Fungal Chemotherapy (five people)

Responsibilities:

Responsible for all aspects of this new group in the development of early stage compounds from screening to the identification and profiling of hit compounds and their further development to being identified as potential lead series. Analyses of SAR data and the active involvement in using this data for further advancement of projects

Project leader of a project comprising a novel natural product antifungal lead series. The project team consisted of ten staff from both the Romainville site and the USA. The major achievement is that this molecule was lead in my Project team to the level of being selected as a clinical candidate. The same molecule was recently completing phase 1 trials following its out-licence to a US based company.

April 1994 – Oct. 1996:

Marion Merrel Dow, Lepetit Research Center, Gerenzano, Italy.  
Scientific Coordinator of the in vitro Medical Microbiology Group  
(six people)

**Responsibilities:**

Responsible for all aspects of this new group in the development of early stage compounds from screening to the identification and profiling of hit compounds and their further development to being identified as potential lead series. Analyses of SAR data and the active involvement in using this data for further advancement of projects

Project leader of a project comprising a novel natural product antibiotic from pre-clinical to late pre-clinical phases of development. The major achievement being that the molecule was finally selected as a clinical candidate. This molecule is now in Phase 3 clinical trials in the US & Europe under licence to another company.

1992 – Dec. 1993:

University of Glasgow, Department of Microbiology, United Kingdom.  
Post-doctoral research fellow; Adhesion of yeasts to prosthetic materials and formation of fungal biofilms on the surface of prosthetic materials

## PROFESSIONAL SOCIETIES

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ASM, SGM, CLSI, EUCAST

## MISCELLANEOUS

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*Compound evaluator.*

- member of the board of evaluators for Current Drugs Iddb database (Internet, Current Drugs Ltd.)
- critical assessment of new antifungal agents in pre-clinical and clinical development.

Reviewer : Reviewer of manuscripts for

- Journal of Clinical Microbiology
- Journal of Chemotherapy.
- Journal of Antimicrobial Chemotherapy
- Infection and Immunity
- Biochemical Pharmacology

## INVITED ORAL PRESENTATIONS

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Iclaprim, A Novel Broad-Spectrum Antibiotic. Antibacterial World Summit, Strategic Research Institute, Princeton, March 2002.

A Novel Antibiotic, Iclaprim: Case Study. SMI Superbugs and Superdrugs March 2003

Sugar Turns Sweet: The Bacterial Phosphotransferase System. Antibacterial World Summit, Strategic Research Institute, Princeton, March 2003.

Iclaprim, A Novel Broad-Spectrum Antibiotic. ECCMID 2003

AR-709: New diaminopyrimidines. Poster Session 225, Oral Summary Presentation, ICAAC 2006

AR-709: A novel antibiotic designed to overcome resistance in streptococci. Superbugs and Superdrugs, April 2007.

Diphenyl ureas, novel class topical antibiotics. ICAAC 2007

## PUBLICATIONS

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1. Stewart, E., Hawser, S.P., and Gow, N.A.R. (1989). Changes in internal and external pH accompanying growth of *Candida albicans*: studies of non-dimorphic variants. *Archives of Microbiology*. 151, 149-153.

2. Hawser, S.P., and Codd, G.A. (1990). Characterization of novel neurotoxicity in *Oscillatoria agardhii*. In: Abstracts of the First European Workshop on the Molecular Biology of the Cyanobacteria. p.19.

3. Hawser, S.P., Beattie, K.A., Lambert, J.J., and Codd, G.A. (1990). Characterization of novel neurotoxicity in *Oscillatoria agardhii* and *Anabaena flos-aquae*. *British Phycological Journal*. 25 (1), 89-90.

4. Lawton, L.A., Hawser, S.P., Jamel Al-Layl, K., Beattie, K.A., Mackintosh, C., and Codd, G.A. (1990). Biological aspects of cyanobacterial microcystin toxins. In: Proceedings of the Second Biennial Water Quality Symposium: Microbiological Aspects. G. Castillo, V. Campos, and L. Herrera (eds.), University of Chile, Santiago, pp. 83-89.

5. Codd, G.A., Lawton, L.A., Beattie, K.A., Edwards, C., and Hawser, S.P. (1991). Cyanobacterial toxins and associated problems in British waters in 1989 and 1990. *British Phycological Journal*. 26 (1), 83.
6. Hawser, S.P., and Codd, G.A. (1991). Action of cyanobacterial microcystin toxins against mammalian cell lines. *British Phycological Journal*. 26 (1), 88.
7. Hawser, S.P., Codd, G.A., Capone, D.G., and Carpenter, E.J. (1991). A neurotoxic factor associated with the bloom-forming cyanobacterium *Trichodesmium*. *Toxicon*. 29, 277-278.
8. Hawser, S.P., and Codd, G.A. (1992). Toxic blue-green algae (cyanobacteria) from brackish- and marine waters. *British Phycological Journal*. 27 (1), 56.
9. Hawser, S.P., and Codd, G.A. (1992). The toxicity of *Trichodesmium* blooms from Caribbean waters. In: *Marine Pelagic Cyanobacteria: Trichodesmium and other Diazotrophs*. E.J. Carpenter, D.G. Capone, and J.G. Rueter (eds.), Kluwer Academic Publishers, Amsterdam, Netherlands, pp. 319-329.
10. Hawser, S.P., O'Neill, J.M., Roman, M.R., and Codd, G.A. (1992). Toxicity of blooms of the cyanobacterium *Trichodesmium* to zooplankton. *Journal of Applied Phycology*. 4, 79-86.
11. Hawser, S.P., and Douglas, L.J. (1993). A model system for *Candida* biofilms. In: *Abstracts of the ASM meeting on Candida and Candidiasis: Biology, Pathogenesis and Management*, abstract A/40. Baltimore, USA.
12. Hawser, S.P., and Douglas, L.J. (1994). Biofilm formation by *Candida* species on the surface of catheter materials in vitro. *Infection and Immunity*. 62, 915-921.
13. Hawser, S.P., and Douglas, L.J. (1995). Resistance of *Candida albicans* biofilms to antifungal agents in vitro. *Antimicrobial Agents and Chemotherapy*. 36, 2128-2131.
14. Hawser, S. (1996). Comparisons of the susceptibilities of planktonic and adherent *Candida albicans* to antifungal agents: a modified XTT tetrazolium assay using synchronised *C. albicans* cells. *Journal of Medical and Veterinary Mycology*. 34, 149-152.
15. Carrano, L., Nalli, M.L., Riva, S., Rossi, R., and Hawser, S. (1996). Adhesion of synchronised *Candida albicans* yeasts to mammalian cells in vitro: effects of antifungal agents. In: *Abstracts of the ASM meeting on Candida and Candidiasis: Biology, Pathogenesis and Management*, abstract A/20. San Diego, USA.
16. Hawser, S., Francolini, M., and Islam, K. (1996). Effects of antifungal agents and enzyme treatments on the adhesion of *Candida albicans* yeasts to plastic. In: *Abstracts of the ASM meeting on Candida and Candidiasis: Biology, Pathogenesis and Management*, abstract A/21. San Diego, USA.
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18. Hawser, S. (1996). Compound evaluation: UK 109,496 (voriconazole). Current Drugs Iddb database.
19. Hawser, S. (1996). Compound evaluation: Sch-56592. Current Drugs Iddb database.
20. Hawser, S., and Islam, K. (1996). Spectrophotometric determination of the morphogenetic transformation by synchronous *Candida albicans*: effects of antifungal agents. *Journal of Antimicrobial Chemotherapy*. 38, 67-73.
21. Hawser, S. (1996). Adhesion of different *Candida* spp. to plastic: XTT formazan determinations. *Journal of Medical and Veterinary Mycology*. 34, 407-410.

22. Hawser, S. (1996). Compound evaluation: Eberconazole. Current Drugs Iddb database.
23. Hawser, S. (1996). Compound evaluation: Rilopirox. Current Drugs Iddb database.
24. Hawser, S. (1996). Compound evaluation: D-0870. Current Drugs Iddb database.
25. Hawser, S., Francolini, M., and Islam, K. (1996). The effects of antifungal agents on the morphogenetic transformation by *Candida albicans* *in vitro*. Journal of Antimicrobial Chemotherapy. 38, 579-587.
26. Hawser, S., and Islam, K. (1997). Review of new azole antifungal agents under development. Current Drugs Iddb Database.
27. Hawser, S. and Islam, K. (1997). Review of new macrocycle antifungal agents under development. Current Drugs Iddb Database
28. Hawser, S., and Islam, K. (1997). Metabolically active *Candida albicans* yeast phase cells bind stereospecifically to immobilized amino acids and to bovine serum albumin. In, Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract F-248, Toronto 28th September - 1st October.
29. Monti, F., S. Hawser, F. Ripamonti, and Islam, K. (1997). Aspirochlorine, a potent and specific inhibitor of fungal protein synthesis. In, Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract F-98, Toronto 28th September - 1st October
30. Hawser, S., and Islam, K. (1998). Binding of *Candida albicans* to immobilized amino acids and bovine serum albumin. Infection and Immunity. 66, 140 - 144.
31. Hawser, S., Baillie, G., and Douglas, L.J. (1998). Production of extracellular matrix by *Candida albicans* biofilms. Journal of Medical Microbiology. 47, 253-256.
32. Hawser, S., H. Plavin, C.J. Jessup, and Ghannoum, M.A. (1998). Comparison of a 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide (XTT) colorimetric method with the standardized national committee for clinical laboratory standards method of testing clinical yeast isolates for susceptibility to antifungal agents. Journal of Clinical Microbiology. 36, 1450 - 1452.
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34. Islam, K. and Hawser, S. (1998). MSI-78 Magainin Pharmaceuticals: Drug Evaluation. Investigational Drugs. 1, 605 - 609.
35. Vértessy, L., W. Aretz, E. Ehlers, S. Hawser, D. Isert, M. Knäuf, M. Kurz, M. Schiell, M. Vogel, and Wink, J. (1998). 3874 H1 and H3, novel antifungal heptaene antibiotics produced by *Streptomyces* sp. HAG 0003874. Journal of Antibiotics. 51, 921-928.
36. Hawser, S., and Islam, K. (1999). Comparisons of the effects of fungicidal and fungistatic antifungal agents on the morphogenetic transformation by *Candida albicans*. Submitted to Journal of Antimicrobial Chemotherapy. 43, 411-413.
37. Islam, K., and Hawser, S. (1999). The effects of antifungal agents on the ability of *Candida albicans* yeasts to bind to immobilized amino acids. Journal of Antimicrobial Chemotherapy. 43, 583-587.
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41. Hawser, S., Haldimann, A., Parisi, S., Gillessen, D., and Islam, K. AR-100, a novel diaminopyrimidine compound: resistance studies in trimethoprim-sensitive and -resistant *Staphylococcus aureus*. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 2002, San Diego, CA. Abstract # F-2028
42. Hawser, S., Weiss, L., Fischer, M., Jaeger, J., Greiveldinger, S., Gillessen, D., Kompis, I., and Islam, K. AR-100, a novel diaminopyrimidine compound: bactericidal activity and post-antibiotic effect on Gram-positive pathogens. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 2002, San Diego, CA. Abstract # F-2029
43. Hammerschlag MR *et al.* *In vitro* activity of Iclaprim, a novel diaminopyrimidine compound, against *Chlamydia trachomatis* and *C. pneumoniae*. 43<sup>rd</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (September 14-17, Chicago) 2003, Abstract E-2001
44. Morrissey I *et al.* Activity of Iclaprim and Comparators Against Atypical Bacterial Respiratory Pathogens. 43<sup>rd</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (September 14-17, Chicago) 2003, Abstract E-2003
45. Hawser S *et al.* A Novel Diaminopyrimidine Antibiotic: *In Vitro* and Intracellular Activity Against *Listeria monocytogenes*. 43<sup>rd</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (September 14-17, Chicago) 2003, Abstract E-2004
46. Zhanel GG *et al.* Activity of Iclaprim Against Penicillin-, Erythromycin-, Trimethoprim/ Sulfamethoxazole- or Ciprofloxacin-Resistant *Streptococcus pneumoniae* from Canada. 43<sup>rd</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (September 14-17, Chicago) 2003, Abstract E-2002
47. Hawser, S., and Islam, K. (2003). Iclaprim, A novel broad-spectrum antibiotic. *Clinical Microbiology and Infection*. 9 (supplement 1)
48. Schneider, P; Hawser, S; and Islam, K. (2003) Iclaprim, a Novel Diaminopyrimidine With Potent Activity on Trimethoprim Sensitive and Resistant Bacteria. *Bioorganic and Medicinal Chemistry Letters*. 13: 4217-4221
49. Kohlhoff, SA, Roblin, PM, Reznik, T, Hawser, S., Islam, K., and Hammerschlag, MR. (2004) *In vitro* activity of a novel diaminopyrimidine compound, iclaprim, against *Chlamydia trachomatis* and *C. pneumoniae*. *Antimicrobial Agents and Chemotherapy*. 48: 1885-1886.
50. Weiss L *et al.* Iclaprim, a novel diaminopyrimidine antibiotic: Synergy studies with different classes of antibiotics. 14<sup>th</sup> European Congress of Clinical Microbiology and Infectious Diseases (May 1-4, Prague) 2004, Abstract P532.

51. Dei-Cas et al. Anti-pneumocystis activity of iclaprim, a reliable therapeutic alternative against *Pneumocystis carinii*. 14<sup>th</sup> European Congress of Clinical Microbiology and Infectious Diseases (May 1-4, Prague) 2004, Abstract P533.
52. Krievens, D., Leighton, A., Brandt, R., Hadvary, P., Hawser, S., Gillesen, D., and Islam, K. (2005). Efficacy and safety of intravenous iclaprim in complicated skin and skin structure infections: Results of a Phase 2 Study. 45<sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (September 14-17, Chicago) 2005, Abstract L-1579. (16-19 December, Washington D.C.)
53. Hawser, S., and Islam, K. (2006) *Candida*. In: *Biofilms, Infection, and Antimicrobial Therapy* Ed. J. Pace. Taylor and Francis, UK
54. Hawser, S., Lociuero, S. and Islam, K. (2006). Dihydrofolate reductase inhibitors as antibacterial agents. *Biochemical Pharmacology*. 71: 941 – 948.
55. Greiveldinger-Poenaru, S. et al. (2006). SAR of novel anti-streptococcal diaminopyrimidine antibiotics and selection of the clinical candidate AR-709. 46<sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract F1-1954. (27 – 30 September, San Francisco).
56. Hawser, S. et al. (2006). AR-709, a novel diaminopyrimidine compound: Bactericidal activity and post-antibiotic effect on Gram-positive pathogens. 46<sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract F1-1959. (27 – 30 September, San Francisco).
57. Hawser, S. et al. (2006). AR-709, a novel diaminopyrimidine compound: Resistance studies in trimethoprim-sensitive and -resistant bacteria. 46<sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract F1-1960. (27 – 30 September, San Francisco).
58. Hawser, S. et al. (2006). Effect of thymidine on the activity of diaminopyrimidine antibacterial agents. 3<sup>rd</sup> International Symposium on resistant Gram-positive infections, Poster CPLA # 28. Niagara-on-the-Lake, Canada (9 – 11 October, 2006).
59. Hawser, S. et al. (2006). In vitro plasma fibrin clot models versus in vivo models of experimental endocarditis: Case study for diaminopyrimidine antibiotics iclaprim and trimethoprim / sulfamethoxazole. 3<sup>rd</sup> International Symposium on resistant Gram-positive infections, Poster CPLA #30. Niagara-on-the-Lake, Canada (9 – 11 October, 2006).
60. Krievens, D. et al. (2006). Efficacy and safety of intravenous iclaprim in complicated skin and skin structure infections: Results of a Phase 2 Study. 3<sup>rd</sup> International Symposium on resistant Gram-positive infections, Poster CPLA #31. Niagara-on-the-Lake, Canada (9 – 11 October, 2006).
61. Hawser, S. et al. (2006). In vitro spectrum of activity of iclaprim against various Gram-positive and Gram-negative pathogens. 3<sup>rd</sup> International Symposium on resistant Gram-positive infections, Poster CPLA #32. Niagara-on-the-Lake, Canada (9 – 11 October, 2006).
62. Hawser, S. et al. (2006). In vitro activity of iclaprim against *Staphylococcus aureus*, Group A and Group B streptococci. 3<sup>rd</sup> International Symposium on resistant Gram-positive infections, Poster CPLA #34. Niagara-on-the-Lake, Canada (9 – 11 October, 2006).
63. Andrews, J. et al (2007). Concentrations in plasma, epithelial lining fluid, alveolar macrophages and bronchial mucosa after a single intravenous dose of 1.6 mg/kg of iclaprim (AR-100) in healthy men. *Journal of Antimicrobial Chemotherapy*. 60: 677 – 680.
64. Morrissey, I and Hawser, S. (2007). Activity of iclaprim against *Legionella pneumophila*. *Journal of Antimicrobial Chemotherapy*, *in press*.

65. Laue, H. et al. Effect of Human Plasma on the Antimicrobial Activity of Iclaprim In Vitro. Journal of Antimicrobial Chemotherapy (*accepted for publication*).

66. Laue, H et al. Activity of the Novel Diaminopyrimidine, Iclaprim, in Combination with Other Antimicrobial Agents. Journal of Antimicrobial Chemotherapy (*accepted for publication*).

## PATENTS

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1. Derivatives of 2-[3-phenyl-2-propenyl]-1,2,3,4-tetrahydro isoquinoline, their process and their use as fungicides. (2000). Babin, D., Braham, A.K., Hawser, S., and Islam, K.. United States Patent 6140340.
2. 2-(3-phenyl-2-propenyl)-1,2,3,4-tetrahydro-isoquinoline derivatives, process for their preparation and their use as fungicides. (2002). Babin, D., Islam, K., Braham, AK, and Hawser, S. PT992502T
3. New 2-(3-phenyl-2-propenyl)-1,2,3,4-tetrahydro-isoquinoline derivatives useful as fungicide for treating e.g. candidoses, cryptococcuses or aspergillooses. (2002). Braham, AK, Hawser, S., Islam, K., and Babin, D. FR2797873.
4. Echinocandin derivatives, method for preparing same and application as antifungal agents. (2006). Fauveau, P. Hawser, S., Lebourg, G. and Schio, L. United States Patent 7022669.
5. Derivatives of echinocandin, their preparation process and their use as antifungals. (2007). Fauveau, P., Hawser, S., Lebourg, G. and Schio, L United States Patent 7192920.

## **EXHIBIT 2**

(19) World Intellectual Property  
Organization  
International Bureau



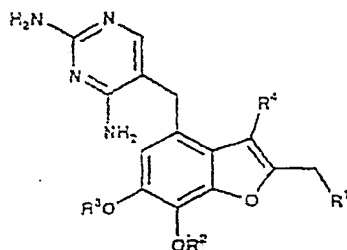
(43) International Publication Date  
20 January 2005 (20.01.2005)

PCT

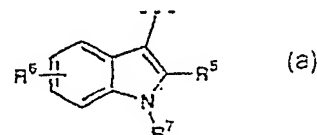
(10) International Publication Number  
WO 2005/005418 A1

- (51) International Patent Classification<sup>7</sup>: C07D 407/14, A61K 31/506, A61P 31/04
- (21) International Application Number:  
PCT/EP2004/007482
- (22) International Filing Date: 8 July 2004 (08.07.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
PCT/EP03/07557 11 July 2003 (11.07.2003) EP
- (71) Applicant (for all designated States except US): ARPIDA AG [CH/CH]; Darmstrasse 36, CH-4142 Münchenstein (CH).
- (72) Inventors; and  
(75) Inventors/Applicants (for US only): GREIVELDINGER-POENARD, Sorana [FR/CH]; Thermenstrasse 19, CH 4310 Rheinfelden (CH). ISLAM, Khalid [GB/CH]; Binningerstrasse 82, CH-4153 Reinach (CH). GILLESSEN, Dieter [CH/CH]; Oberfeldstrasse 12, CH-4153 Pratteln (CH). BURRI, Kaspar [CH/CH]; Höhenweg 47, CH-4102 Binningen (CH).
- (74) Agent: HOFMANN, Dieter; Thewilerstrasse 87, CH-4153 Reinach (CH).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SI, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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(54) Title: BENZOFURAN DERIVATIVES AND THEIR USE IN THE TREATMENT OF MICROBIAL INFECTIONS



(1)



(2)

(57) Abstract: The invention relates to new benzofuran derivatives of the general formula 1 and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as anti-infectives.

General Procedure E: Measurement of antimicrobial activity

Antimicrobial susceptibility testing was performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) procedure [M7-A5, 2001].

- 5 M7-A5 (2001): Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard —Fifth Edition American National Standard. The minimal inhibition concentration (MIC) of the compounds regarding resistant strains is in the range of 0.25-2.0 µg/mL depending on the strain used.

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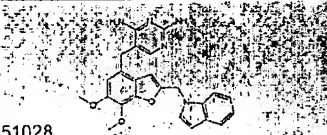
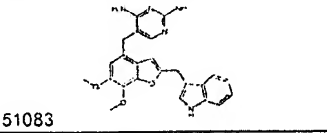
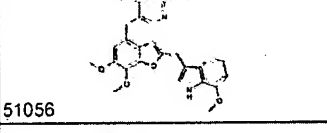
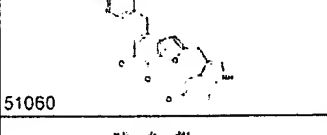
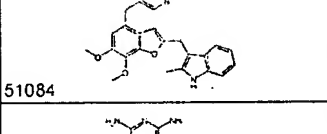
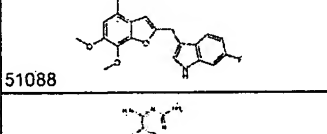
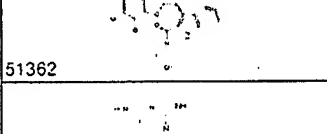
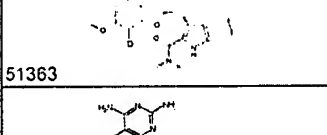
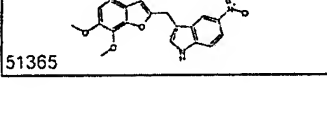
General Procedure F: Purified Enzymes and DHFR Enzyme Assay:

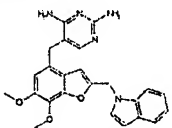
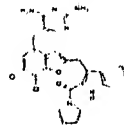
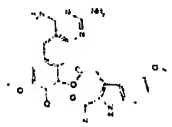
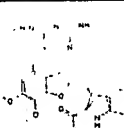
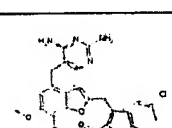
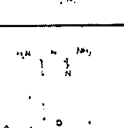
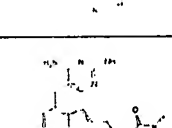
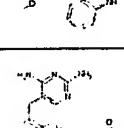
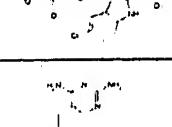
Bacterial and human dihydrofolate reductases were purified, shown to be functional and used in DHFR assays as described by Baccanari & Joyner (Baccanari, D.P. and Joyner, S.S. 1931. Dihydrofolate reductase hysteresis and its effect on inhibitor binding analyses. Biochem. 20, 1710-1716)

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The IC<sub>50</sub> of the compounds regarding DHFR mutants is in the range of 0.5-8.0 µM.

## **EXHIBIT 3**

Structure	Example Number	Name	MIC µg/mL
			<i>Streptococcus pneumoniae</i> 49619
 51028	WO02/10156 p.6 l.14 WO02/10157 p.9 l.24	5-[2-(1H-indol-3-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine	2
 51083	EXP6	5-[2-(1H-indol-3-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;	<0.125
 51056	EXP7	5-[6,7-Dimethoxy-2-(7-methoxy-1H-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;	<0.125
 51060	EXP8	5-[6,7-Dimethoxy-2-(5-methoxy-1H-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;	<0.125
 51084	EXP9	5-[6,7-Dimethoxy-2-(2-methyl-1H-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;	0.5
 51088	EXP10	5-[2-(6-Fluoro-1H-indol-3-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;	<0.125
 51362	EXP11	{3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indol-2-yl}-morpholin-4-yl-methanone;	0.125
 51363	EXP12	3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid dimethylamide;	0.125
 51365	EXP13	5-[6,7-Dimethoxy-2-(5-nitro-1H-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;	<0.125

Structure	Example Number	Name	MIC µg/mL
			<i>Streptococcus pneumoniae</i> 49619
 51028	WO02/10156 p.6 l.14 WO02/10157 p.9 l.24	5-[2-(Indol-1-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine	2
 51371	EXP14	3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indol-2-yl)-pyrrolidin-1-yl-methanone	0.25
 51372	EXP15	3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-5-methoxy-1H-indole-2-carboxylic acid dimethylamide	<0.125
 51390	EXP16	3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid methoxy-methyl-amide;	<0.125
 51391	EXP17	5-Chloro-3-[4-(2,4-diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid dimethylamide;	<0.125
 51392	EXP18	3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-5-fluoro-1H-indole-2-carboxylic acid dimethylamide;	<0.125
 51511	EXP19	3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid N,N'-dimethyl-hydrazide;	<0.125
 51510	EXP20	5-Chloro-3-[4-(2,4-diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid methoxy-methyl-amide;	<0.125
 51515	EXP21	3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-5-fluoro-1H-indole-2-carboxylic acid methoxy-methyl-amide;	0.125